PATENT COOPERATION TREATY

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INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/000243	03.02.2004	04.02.2003

International Patent Classification (IPC) or both national classification and IPC
A61K49/22, A61K49/18, A61K9/19

Applicant
BRACCO RESEARCH SA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Venturini, F Telephone No. +49 89 2399-7847

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/000243

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-34
	No:	Claims	1,35-40
Inventive step (IS)	Yes:	Claims	2-34
	No:	Claims	1,35-40
Industrial applicability (IA)	Yes:	Claims	1-38
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

SECTION III

Claims 39,40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

SECTION V

The following documents are referred to in the present opinion. If not otherwise specified reference is made to the relevant passages cited in the International Search Report.

D1: WO 99/08716 A (MARSDEN JOHN CHRISTOPHER ; OMTVEIT TORE (NO); NYCOMED IMAGING AS (NO)) 25 February 1999 (1999-02-25)
D2: EP-A-1 228 770 (BRACCO RES S A) 7 August 2002 (2002-08-07)
D3: WO 98/05364 A (MARSDEN JOHN CHRISTOPHER ; BRAENDEN JORUNN (NO); DUGSTAD HARALD (NO);) 12 February 1998 (1998-02-12)
D4: US-B-6 280 7051 (KLEIN DAVID H ET AL) 28 August 2001 (2001-08-28)
D5: US-A-6 146 657 (MATSUNAGA TERRY ET AL) 14 November 2000 (2000-11-14)
D6: WO 96/09037 A (LIPOSOME CO INC) 28 March 1996 (1996-03-28)
D7: WO 97/40858 A (IMARX PHARMACEUTICAL CORP) 6 November 1997 (1997-11-06)
D8: SCHNEIDER M ET AL: "BR1: A NEW ULTRASONOGRAPHIC CONTRAST AGENT BASED ON SULFUR HEXAFLUORIDE-FILLED MICROBUBBLES" INVESTIGATIVE RADIOLOGY, PHILADELPHIA, PA, US, vol. 30, no. 8, 1 August 1995 (1995-08-01), pages 451-457, XP000611270
D9: WO 99/36104 A (DU PONT PHARM CO) 22 July 1999 (1999-07-22)
D10: EP-A-1 419 789 (BRISTOL MYERS SQUIBB PHARMA CO) 19 May 2004 (2004-05-19)
D11: US 2002/102217 A1 (HELLEBUST HALLDIS ET AL) 1 August 2002 (2002-08-01)

D1 describes a process for the production of fluorocarbon-containing lyophilized

contrast agent starting from a dispersion of gas microbubbles in an aqueous medium containing a membrane-forming lipid. said microbubbles fall under the description of claim 35 of the present application.
D2 describes a contrast agent comprising gas-filled microbubbles which contain phospholipid. The size of said micro bubbles is very close to the size of the micro bubbles claimed in the present application (see Table 1).
D3 deals with micro bubbles filled with biocompatible gas and stabilized by phospholipid. Also said micro bubbles fall under the description of claim 35 of the present application.
D4 deals with a composition which upon reconstitution forms a gas emulsion comprising micro bubbles which range in size from 1 to 20 µm, whereby no mean value is given.
D5 deals with gas-filled liposomes. The size of said liposomes appears to be very close to those described in the present application (see table 5).
D11 deals with diagnostic and therapeutic agents. In example 11 a method is given for the production of an emulsion and subsequent lyophilization which fall under the description of claim 1 of the present application.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 35-40 is not new in the sense of Article 33(2) PCT.
The present application discloses gas-filled micro bubbles which are either falling under the description of the available prior art or so close to those values that, due to the different measure techniques and the experimental error, it appears impossible to clearly differentiate said micro bubbles from the cited prior art.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 35-40 does not involve an inventive step in the sense of Article 33(3) PCT. The problem to be solved by the present application may be formulated as how to provide an alternative formulation of gas-filled micro bubbles comprising phospholipid. The solution proposed in the present application is to provide micro bubbles which have a number mean diameter of less than 1,7 µm and a volume median diameter such that the volume median diameter/number mean diameter ratio is about 2.00 or lower. However, the available prior art already discloses such micro bubbles and the subject-matter of claims 35-40 is therefore not inventive.
Moreover, claim 1 refers to a method of preparation which s not new and cannot therefore be considered inventive.
The subject-matter of independent claim 1 is already known. If the novelty objection can

not be overcome the requisite unity of invention (Rule 13.1 PCT) therefore may no longer exist inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the following groups of dependent claims: 1 and dependent claims and claim 35 and dependent claims.

For the assessment of the present claims 39,40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.